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Hydroxyethyl starch 130/0.4 compared to 0.9% NaCl administered to greyhounds with haemorrhagic shock

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Running head: Hydroxyethyl starch in canine haemorrhagic shock
Abstract

Objective To determine the cardiovascular and acid-base effects of 6% hydroxyethyl starch (HES) 130/0.4 and 0.9% sodium chloride (NaCl) administered to anaesthetized greyhounds with haemorrhagic shock.

Study design Prospective, experimental, complete randomized block design.

Animals Twelve healthy adult greyhounds.

Methods After 60 minutes of isoflurane anaesthesia, 48 mL kg\(^{-1}\) of blood was removed to induce hypotension. Dogs were randomized to receive either 20 mL kg\(^{-1}\) of HES 130/0.4 or 80 mL kg\(^{-1}\) of 0.9% NaCl over 20 minutes. Haemoglobin, arterial and central venous blood gas and electrolytes, lactate, mean arterial pressure (MAP), and cardiac index were measured at: T0, 60 minutes after induction of anaesthesia, immediately prior to blood removal; T1, immediately after blood removal; T2, immediately after fluid administration; and T3, 40 minutes after fluid administration. Oxygen extraction ratio (O\(_2\)ER) was calculated at each sample time.

Results Oxygen extraction ratio increased at T1 and decreased at T2 and T3, with no difference between the two groups. Dogs administered HES 130/0.4 had higher lactate at T2 [mean (95% confidence interval) 1.3 (0.8 - 1.9) mmol L\(^{-1}\)] than dogs administered 0.9% NaCl [0.8 (0.5 - 1.1) mmol L\(^{-1}\)]; \(p = 0.045\). Dogs administered HES 130/0.4 had a higher MAP at T3 [88 (74-102) mmHg] than dogs administered 0.9% NaCl [69 (60-79) mmHg]; \(p = 0.019\). Dogs administered 0.9% NaCl were more acidaemic at T2 and T3, including higher hydrogen ion, lower bicarbonate, lower base excess, and higher chloride concentrations.

Conclusion and clinical relevance The effect of 20 mL kg\(^{-1}\) of HES 130/0.4 on shock, as measured by O\(_2\)ER, was no different than 80 mL kg\(^{-1}\) of 0.9% NaCl in dogs under general
anaesthesia. Acidaemia in the NaCl group is likely attributable to a hyperchloremic metabolic acidosis from the larger volume administered.

**Keywords** acid-base balance, fluid therapy, haemorrhage, Hydroxyethyl starch 130/0.4, shock

**Introduction**

Hypovolaemic shock secondary to haemorrhage is a known complication of surgery (Gaynor et al. 1999) and trauma (Bishop et al. 1993) that can result in organ dysfunction and death (Bishop et al. 1993; Mythen and Webb 1994). Rapid expansion of intravascular volume with fluid therapy is an important first step in minimizing organ dysfunction (Bishop et al. 1995). As haemorrhage reduces total protein and oncotic pressure, artificial colloid solutions that increase oncotic pressure can be administered for blood volume expansion (Haupt and Rackow 1982; James et al. 2004; Silverstein et al. 2005; Aarnes et al. 2009; Lobo et al. 2010). Artificial colloid solutions such as hydroxyethyl starch (HES) 130/0.4 have produced equal or greater increases in haemodynamic function compared to similar doses of crystalloid solutions in people with shock (Ferreira et al. 2005; Gondos et al. 2010; Lobo et al. 2010).

One study in splenectomized dogs with haemorrhagic shock under general anaesthesia showed no difference in cardiovascular parameters after administration of 28 mL kg\(^{-1}\) of HES 130/0.4 compared to 84 mL kg\(^{-1}\) of lactated Ringers solution (LRS) (Barros et al. 2011). As splenic contraction is an important compensatory mechanism in the resolution of shock in dogs (Hsia et al. 2007), this study does not accurately demonstrate the response to different fluid types in the clinical setting. In addition, this study used a ratio of the volume of colloid fluid to crystalloid fluid of 1:3, whereas the current recommendations of colloid fluid to crystalloid fluid ratio for dogs is 1:4. This recommendation is based on an earlier study which
found there was no difference in blood volume expansion with the administration of 20 mL kg\(^{-1}\) of HES 670/0.75 or 80 mL kg\(^{-1}\) of 0.9% sodium chloride (NaCl) in a euvolaemic canine model, 30 minutes after redistribution of fluids (Silverstein et al. 2005). Also, the study by Barros et al. used LRS as a comparison solution whereas HES 130/0.4 is most commonly suspended in 0.9% NaCl. Administration of large volumes of 0.9% NaCl may cause metabolic acidosis (Scheingraber, 1999). Therefore, a more appropriate crystalloid comparison in regards to assessing the cardiovascular and acid-base effects of HES 130/0.4 would be 0.9% NaCl.

The objective of this study was to determine the cardiovascular and acid-base effects of a clinically relevant dose of HES 130/0.4 administered to greyhounds with haemorrhagic shock under general anaesthesia. This study was designed to test the hypothesis that cardiovascular, haemodilution and acid-base parameters will be different after administration of 20 mL kg\(^{-1}\) of HES 130/0.4 compared to 80 mL kg\(^{-1}\) of 0.9% NaCl. The null hypothesis was that there is no difference between treatments.

### Materials and methods

This study was part of a larger project (McBride et al. 2016) and was approved by the Murdoch University Animal Ethics Committee (2398/11). Twelve adult greyhound dogs deemed healthy based on physical examination and complete blood count were included. The dogs were not fasted and had free access to water. Each dog was assigned to receive either HES 130/0.4 \((n = 6)\) or 0.9% NaCl \((n = 6)\) based on selection of a sealed envelope designating treatment. We estimated that a sample size of 6 would give us 80% power \((\alpha = 0.05)\) to detect an effect size of 0.6 between the two groups with all parameters, with the distribution of data estimated from a previous study (Raisis et al. 2015).
The dogs were premedicated with 0.2 mg kg\(^{-1}\) of methadone (Methone, Parnell Australia Pty Ltd, Australia) given intramuscularly. Thirty minutes after premedication, a 20-gauge 1-inch over-the-needle catheter was aseptically placed in the right cephalic vein, and anaesthesia was induced with 2.5 mg kg\(^{-1}\) of alfaxalone (Alfaxan, Jurox Pty Ltd, Australia) given intravenously. Animals were placed in left lateral recumbency, orotracheally intubated and anaesthesia was maintained with isoflurane (ISO Veterinary Companies of Australia, Australia) delivered in up to 98% oxygen via a circle breathing system. Vaporizer settings were adjusted to achieve an end-tidal isoflurane concentration of 1.4% measured using an agent monitor (Capnomac Ultima, Darex-Ohmeda Medical Supplies Australia, Australia). Mechanical ventilation was provided using a volume-controlled time-cycled ventilator (Model TH-1 Beijing Read Eagle Technology Co Ltd, China) at a rate of 10 breaths minute\(^{-1}\) with an initial tidal volume of 20 mL kg\(^{-1}\). This was adjusted according to blood gas measurement at the end of the instrumentation period, to achieve an arterial carbon dioxide tension of PaCO\(_2\) 35 - 40 mmHg (4.7 – 5.3 kPa) in all dogs. No further adjustment was made throughout the remainder of anaesthesia. Hartmann’s solution (Baxter Healthcare Pty Ltd Australia, Australia) was administered via the cephalic catheter at a rate of 10 mL kg hour\(^{-1}\) until the time of administration of the treatment solutions. A 12-gauge 6-inch over-the-needle catheter was aseptically placed in the right jugular vein, with the distal end premeasured to be placed beyond the thoracic inlet, palpated as the cranial aspect of the first sternebra. A 14-gauge 2-inch over-the-needle catheter was surgically placed in the left femoral artery. The catheters were connected via fluid filled transducers (DTX Plus Argon Critical Care Systems, Singapore) to a multivariable monitor (Surgivet V9203 Sound Medical, Australia) and calibrated to atmospheric pressure. Heart rate (HR), electrocardiogram, central venous pressure (CVP), and pulse oximetry were monitored with the multivariable monitor throughout the experiment. Body temperature was maintained between 36 and 38 \(\degree C\) by
applying warm air to the right lateral surface of the dog (Bair Hugger warming unit Model 505, Critical Assist, Australia).

Sixty minutes after induction of anaesthesia, haemorrhagic shock was induced by removing 48 mL kg\(^{-1}\) of blood over a 30 minute period from the femoral arterial catheter. Blood was collected into sterile blood collection bags and donated to the hospital’s blood bank for clinical use. The volume of blood removal was chosen based on preliminary data showing that removal of this amount of blood was required in order to reliably induce clinically relevant hypotension in greyhounds (Raisis et al. 2015). Following removal of 48 mL kg\(^{-1}\) of blood, intravenous Hartmann’s solution administration was discontinued and the dogs were administered either 20 mL kg\(^{-1}\) of HES 130/0.4 (Voluven 6% hydroxyethyl starch 130/0.4, Fresnius Kabi Deutschland GmbH, Germany) or 80 mL kg\(^{-1}\) of 0.9% NaCl intravenously over 20 minutes. These doses were chosen based on a previous study in a euvolaemic model (Silverstein et al. 2005). Hydroxyethyl starch 130/0.4 was delivered using a pressure bag via the cephalic catheter and 0.9% NaCl was delivered using two pressure bags via the cephalic and jugular catheters. The pressure applied to each bag was monitored throughout to ensure the fluid was delivered continuously during the 20 minute period.

Data for analysis was collected at four time points (Fig. 1): T0, at baseline 60 minutes after induction, immediately prior to haemorrhage; T1, immediately after removing 48 mL kg\(^{-1}\) of blood over 30 minutes; T2, immediately after administration of 20 mL kg\(^{-1}\) of HES 130/0.4 or 80 mL kg\(^{-1}\) of 0.9% NaCl over 20 minutes; and T3, 40 minutes after completion of respective fluid administration. At each time point, blood was collected simultaneously from the femoral arterial and jugular venous catheters into lithium heparin syringes. Arterial and venous blood gas analysis and arterial lactate, sodium, chloride, and haemoglobin (Hb) concentrations were measured using the radiometer (ABL 725 Radiometer Pacific Pty Ltd, Australia). Manual packed cell volume measurement was also performed within five minutes of blood collection.
Immediately following blood collection, cardiac output (CO) was measured in duplicate using the lithium dilution (LiDCO Cardiac Sensor Systems, LiDCO Ltd, UK) technique (LiDCO) as previously described, (Shih et al. 2011) with modification of the dose of lithium chloride to 0.005 mmol kg\(^{-1}\) (Raisis et al. 2015) injected via the central venous catheter and withdrawing blood via the femoral artery. Sodium and Hb concentration were required for calculation of CO measurement. When two results varied greater than 10%, repeated measurements were made and the results varying greater than 10% were excluded from analysis. Simultaneously at the four time points, HR, direct MAP, and CVP were measured. The \(O_2\)ER was calculated at each time point using the formulae in Table 1, which also includes all calculations required to calculate \(O_2\)ER.

At the conclusion of data collection, euthanasia was performed using intravenous pentobarbital.

**Statistical method**

All responses were tested for normality and found to follow a normal distribution with failure to reject the null hypothesis of normality at \(p < 0.05\) using the Shapiro-Wilk statistic. Response data was summarized and reported as mean (95% confidence intervals).

Descriptive data of each group cohort are reported as mean ± standard deviation (SD). All responses were tested for a fixed effect of treatment (HES 130/0.4, 0.9% NaCl) and time (T0 - T3) using a mixed linear model that included the random variance of dog nested within group. Where there was a significant effect of group, post-hoc comparisons were made between groups at each time point using Scheffe’s adjustment with adjusted \(p\) values reported, considered significant at \(p < 0.05\). Age, body weight and body surface area were compared across groups using a t-test with \(p < 0.05\) considered significant. SAS v 9.4 (SAS Institute, NC, USA) was used for the analysis.
Results

Each group had three male and three female dogs. The body weight was 28.3 ± 3.9 kg for the HES 130/0.4 group and 28.3 ± 2.6 kg for the 0.9% NaCl group. The age was 3 ± 2 and 4 ± 2 years, respectively. There was no significant difference in body weight or age of the dogs across the two groups.

Haemorrhage resulted in an increase in O$_2$ER consistent with shock in both groups (Table 2). Both fluids reduced O$_2$ER to baseline levels, with no significant differences between the two groups at any time point. Dogs administered HES 130/0.4 had a higher VO$_2$ ($p = 0.01$) and Hb concentration ($p < 0.001$) at T2, and a higher MAP ($p = 0.019$) at T3 than dogs administered 0.9% NaCl. There was no significant difference between the two groups for any other cardiovascular or oxygen transport variables.

At T0, dogs administered 0.9% NaCl had a higher hydrogen ion concentration ($p = 0.021$) compared to dogs administered HES 130/0.4 (Table 3). At T2 and T3, dogs administered 0.9% NaCl had a higher hydrogen ion concentration ($p = 0.03$, $p = 0.017$, respectively), lower bicarbonate concentration ($p = 0.002$, $p < 0.001$, respectively), lower base excess concentration ($p = 0.001$, $p < 0.0001$, respectively), and higher chloride concentration ($p < 0.001$, $p = 0.001$, respectively) compared to dogs administered HES 130/0.4. Dogs administered HES 130/0.4 had a marginally higher lactate concentration at T2 ($p = 0.045$). There was no significant difference between the two groups at other time points and with other values.

Discussion

This study demonstrated that 20 mL kg$^{-1}$ of HES 130/0.4 and 80 mL kg$^{-1}$ of 0.9% NaCl administered over 20 minutes were both effective in decreasing O$_2$ER in greyhounds in shock.
under anaesthesia, with no difference between the two groups. While 80 mL kg\(^{-1}\) of 0.9% NaCl administration resulted in a hyperchloraemic metabolic acidosis persisting for 40 minutes (T3), 20 mL kg\(^{-1}\) of HES 130/0.4 administration did not. Some differences were also found immediately after fluid administration (T2). Dogs administered 0.9% NaCl had lower Hb concentration and VO\(_2\), likely the result of the greater amount of fluid administered and hence greater blood volume expansion at this time point. This change in Hb concentration was not present by T3, which can be explained by greater fluid redistribution during this time period, compared to dogs administered HES 130/0.4.

Oxygen extraction ratio is an objective measure of tissue oxygen utilization, and is an earlier marker of shock compared to other variables such as lactate (Ronco et al. 1993). Oxygen extraction ratio is the amount of oxygen consumed by cells (VO\(_2\)) in proportion to oxygen delivered (DO\(_2\)). As DO\(_2\) is usually surplus to need, VO\(_2\) and O\(_2\)ER are usually maintained within normal limits despite mild decreases in DO\(_2\). When DO\(_2\) is decreased to a level that VO\(_2\) becomes dependent on the amount of oxygen delivered, a decrease in VO\(_2\) and a rapid increase in O\(_2\)ER is usually observed (Haskins et al. 2005). An interesting observation in our study was an increase in VO\(_2\) during shock rather than a decrease in VO\(_2\). This also has been observed in other studies in anaesthetized dogs (Yoo et al. 2007; Barros et al. 2011). One possible explanation for this is reduced ability for vasoconstriction during haemorrhagic shock while anaesthetized with isoflurane, a known vasodilatory agent (Schwinn et al. 1990). This can result in increased availability of capillary beds for oxygen exchange and increased VO\(_2\). Another explanation could be recruitment of capillary beds and increased cellular metabolism in muscle resulting from increased catecholamine levels (Schlichtig et al. 1991). Interestingly, VO\(_2\) was significantly higher after HES 130/0.4 administration at T2. This is likely the result of less blood volume expansion at this time point, and it may be that an increase in VO\(_2\) is typical for dogs in shock under anaesthesia.
Although there was no difference in \( \text{O}_2 \text{ER} \) across dogs in each group, other variables including Hb and lactate concentrations were significantly different at T2. Haemoglobin concentration was significantly higher at T2 in dogs administered HES 130/0.4 indicating less blood volume expansion (Dill & Costill 1974), most likely the result of the difference in administered volumes. Forty minutes after fluid administration however, there was no difference in Hb concentration across between groups, which has also been observed with other HES solutions (Lamke & Liljedahl 1976; Silverstein et al. 2005). Another explanation for differences in haemoglobin between groups is individual variability in splenic contraction during hypovolaemia (Hsia et al. 2007). Lactate concentration was also significantly higher at T2 in dogs administered HES 130/0.4 but given the difference was marginal, it is considered clinically irrelevant. Small differences in lactate concentration may be attributable to differences in haemodilution, or lactate metabolism and clearance (Tashkin et al. 1972).

The other major difference across dogs was the acid-base balance. Dogs administered 0.9% NaCl developed a hyperchloraemic metabolic acidosis, which persisted 40 minutes after fluid administration. The degree of the hyperchloraemic metabolic acidosis in these dogs is likely attributable to the larger volume administered. Curiously, this effect persisted at T3 in the dogs administered 0.9% NaCl despite there being no difference in haemodilution between the two groups at this time point. Although metabolic acidosis can have a negative impact on vasomotor tone (Capellini et al. 2013) and myocardial function (Mayoux et al. 1994), this was not reflected in a significant difference in systemic vascular resistance index SVRI or CI at T3. However, subtle differences in these variables may be one reason why dogs that administered 0.9% NaCl had a lower MAP at T3 when the effects where combined.

Although the results suggest that the effect of 20 mL kg\(^{-1}\) of HES 130/0.4 was no different to 80 mL kg\(^{-1}\) of 0.9% NaCl on shock as measured by \( \text{O}_2 \text{ER} \), when selecting fluid types,
potential adverse effects should be considered. Hydroxyethyl starch 130/0.4 has been
associated with acute kidney injury in people with severe sepsis and septic shock (Brunkhorst & Oppert 2008; Guidet et al. 2012; Myburgh et al. 2012b; Perner et al. 2012) and increased
bleeding and transfusion requirements (Franz et al. 2001; Deusch et al. 2003; Myburgh et al.
2012a). Although experimental studies showed that HES 130/0.4 did not cause significant
platelet dysfunction in vitro (Wurlod et al. 2015; McBride et al. 2013) or in vivo in dogs
(McBride et al. 2016) large scale prospective clinical trials are required to determine if an
increased risk of bleeding and acute kidney injury exists in dogs treated in the clinical setting.

One of the limitations of this study is the greyhound model. Greyhounds are known to have
different haemodynamic variables compared to non-greyhound breeds, including higher
resting MAP, CO, SVRI (Cox et al. 1976), and blood volume (Cortice 1943) compared to
other dogs. Although the difference in haemodynamic and splenic response to acute
haemorrhage between greyhound and other breeds has not been previously compared, there
may be some differences. Greyhounds also have higher haematocrit values (Zaldivar-Lopez
et al. 2011b), which will affect blood viscosity and haemodynamics (Levy & Share 1953). In
addition, differences in haematocrit will also directly affect O$_2$ER. Blood gas and co-
oximetry values are also different in greyhounds including higher pH, arterial oxygen content
of blood, and arterial oxygen saturation, which will also influence O$_2$ER (Zaldivar-Lopez et
al. 2011a). Therefore, absolute values in this study cannot be directly extrapolated to other
dog breeds.

This study only had a sample size of six in an unpaired design, and type II error may be
responsible for conclusions of no difference. Perhaps of most interest would be the lack of
difference in O$_2$ER, where sample sizes of 193 and 770 dogs would be required to detect the
differences recorded between treatments at T2 and T3, respectively. Although there was
moderate variance, the effect sizes at these time points were small (0.25 to 0.5) and less than
what was used to estimate sample size. Differences reflecting this smaller effect size are unlikely to be of clinical relevance. Therefore, if a small difference does exist, it is likely not worth pursuing with a larger sample size based on the results of this study.

In conclusion, administration of 20 mL kg\(^{-1}\) of HES 130/0.4 and 80 mL kg\(^{-1}\) of 0.9% NaCl resulted in decreases in O\(_2\)ER to within normal canine reference intervals with no difference between dogs receiving either treatment. This information may help to guide fluid bolus volume choice, depending on fluid type, in clinical patients. Although there may have been greater blood volume expansion immediately after administration of 80 mL kg\(^{-1}\) of 0.9% NaCl, HES 130/0.4 resulted in a slightly higher MAP 40 minutes after administration. Administration of HES 130/0.4 also resulted in less acidaemia. Future clinical research is needed to characterise the clinical relevance of any adverse effects of both high-chloride fluids and HES fluid preparations.

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**Authors’ contributions**

DM: Study design, acquisition of data, interpretation of data, manuscript preparation, manuscript revision; AR: Study design, acquisition of data, interpretation of data, manuscript revision; GH: Study design, statistical methods, statistical analysis, interpretation of data, manuscript revision; LS: Study design, interpretation of data, manuscript preparation, manuscript revision.

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Figure Legends

**Figure 1** Time-line of study protocol for fluid administration and data collection from 12 anaesthetised greyhounds at four time points: T0, 60 minutes after induction of anaesthesia, immediately prior to blood removal; T1, during haemorrhagic shock, after removing 48 mL kg\(^{-1}\) of blood; T2, immediately after fluid administration of 20 mL kg\(^{-1}\) of hydroxyethyl starch (HES)130/0.4 or 80 mL kg\(^{-1}\) of 0.9% sodium chloride (NaCl) over 20 minutes; and T3, 40 minutes after completion of respective fluid administration.
Table 1 Formulas required to calculate oxygen extraction ratio (Haskins et al. 2005).

<table>
<thead>
<tr>
<th>Calculated variable (units)</th>
<th>Abbreviation</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial oxygen content (mL dL$^{-1}$)</td>
<td>CaO$_2$</td>
<td>(1.34 x Hb x SaO$_2$) + (0.003 x PaO$_2$)</td>
</tr>
<tr>
<td>Venous oxygen content (mL dL$^{-1}$)</td>
<td>CvO$_2$</td>
<td>(1.34 x Hb x SvO$_2$) + (0.003 x PvO$_2$)</td>
</tr>
<tr>
<td>Cardiac index (L minute$^{-1}$ m$^{-2}$)</td>
<td>CI</td>
<td>CO/BSA</td>
</tr>
<tr>
<td>Systemic vascular resistance index (dynes.sec.cm$^{-5}$ m$^{-2}$)</td>
<td>SVRI</td>
<td>((MAP – CVP)79.92)/CI</td>
</tr>
<tr>
<td>Oxygen delivery index (mL minute$^{-1}$ m$^{-2}$)</td>
<td>DO$_2$</td>
<td>CaO$_2$ x CI x 10</td>
</tr>
<tr>
<td>Oxygen consumption index (mL minute$^{-1}$ m$^{-2}$)</td>
<td>VO$_2$</td>
<td>(CaO$_2$ – CvO$_2$) x CI x 10</td>
</tr>
<tr>
<td>Oxygen extraction ratio (%)</td>
<td>O$_2$ER</td>
<td>VO$_2$/DO$_2$ x 100</td>
</tr>
<tr>
<td>Body surface area (m$^2$)</td>
<td>BSA</td>
<td>(10.1 x body weight$^{0.67}$) x 10$^{-4}$</td>
</tr>
</tbody>
</table>

Haemoglobin concentration (Hb), arterial oxyhaemoglobin saturation (SaO$_2$), partial pressure of oxygen in arterial blood (PaO$_2$), venous oxyhaemoglobin saturation (SvO$_2$), partial pressure of oxygen in venous blood (PvO$_2$), cardiac output (CO), mean arterial pressure (MAP), central venous pressure (CVP)
Table 2 Mean and 95% confidence interval of cardiovascular and oxygen (O₂) transport variables in 12 anaesthetised greyhounds at four time points: T0, baseline; T1, during haemorrhagic shock, after removing 48 mL kg⁻¹ of blood; T2, immediately after administration of 20 mL kg⁻¹ of hydroxyethyl starch (HES) 130/0.4 or 80 mL kg⁻¹ of 0.9% sodium chloride (NaCl) over 20 minutes; and T3, 40 minutes after completion of respective fluid administration.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (g L⁻¹)</td>
<td>0.9% NaCl</td>
<td>17.5 (16.1–18.8)</td>
<td>16.8 (15.7–17.9)</td>
<td>8.6 (7.8–9.5)</td>
<td>11.1 (9.9–12.2)</td>
</tr>
<tr>
<td></td>
<td>HES 130/0.4</td>
<td>18.3 (17.0–19.6)</td>
<td>16.8 (15.9–17.6)</td>
<td>11.5 (10.8–12.2)*</td>
<td>10.5 (9.7–11.4)</td>
</tr>
<tr>
<td>Heart rate (beats minute⁻¹)</td>
<td>0.9% NaCl</td>
<td>82 (63-102)</td>
<td>151 (124-179)</td>
<td>117 (105-129)</td>
<td>119 (103-135)</td>
</tr>
<tr>
<td></td>
<td>HES 130/0.4</td>
<td>75 (69-82)</td>
<td>157 (134-181)</td>
<td>124 (105-143)</td>
<td>122 (99-145)</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>0.9% NaCl</td>
<td>80 (69-91)</td>
<td>36 (26-47)</td>
<td>71 (57-85)</td>
<td>69 (60-79)</td>
</tr>
<tr>
<td></td>
<td>HES 130/0.4</td>
<td>81 (70-91)</td>
<td>36 (23-48)</td>
<td>86 (72-100)</td>
<td>88 (74-102)*</td>
</tr>
<tr>
<td>Central venous pressure</td>
<td>0.9% NaCl</td>
<td>5.2 (3.4-7.0)</td>
<td>-0.7 (-2.8-1.5)</td>
<td>5.2 (1.6-8.8)</td>
<td>3.2 (1.0-5.3)</td>
</tr>
<tr>
<td>(mmHg)</td>
<td>HES 130/0.4</td>
<td>4.0 (3.3-4.7)</td>
<td>-1.3 (-3.2-0.5)</td>
<td>2.7 (0.4-4.9)</td>
<td>2.8 (1.6-4.1)</td>
</tr>
<tr>
<td>-------------</td>
<td>-------------</td>
<td>---------------</td>
<td>-----------------</td>
<td>--------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Cardiac index (L minute⁻¹ m⁻²)</td>
<td>0.9% NaCl</td>
<td>3.7 (2.7-4.6)</td>
<td>1.8 (1.3-2.3)</td>
<td>4.3 (3.4-5.1)</td>
<td>4.1 (3.6-4.6)</td>
</tr>
<tr>
<td></td>
<td>HES 130/0.4</td>
<td>3.7 (2.9-4.5)</td>
<td>1.5 (1.0-2.0)</td>
<td>5.1 (3.1-7.0)</td>
<td>5.3 (3.2-7.5)</td>
</tr>
<tr>
<td>Systemic vascular resistance index (dynes.sec.cm⁻⁵ m⁻²)</td>
<td>0.9% NaCl</td>
<td>1708 (1229-2187)</td>
<td>1690 (1262-2118)</td>
<td>1235 (994-1476)</td>
<td>1305 (1054-1557)</td>
</tr>
<tr>
<td></td>
<td>HES 130/0.4</td>
<td>1691 (1452-1930)</td>
<td>1995 (1567-2423)</td>
<td>1411 (1025-1798)</td>
<td>1350 (1036-1664)</td>
</tr>
<tr>
<td>O₂ delivery (mL minute⁻¹ m⁻²)</td>
<td>0.9% NaCl</td>
<td>931 (651-1212)</td>
<td>435 (288-582)</td>
<td>567 (462-673)</td>
<td>680 (553-807)</td>
</tr>
<tr>
<td></td>
<td>HES 130/0.4</td>
<td>968 (780-1155)</td>
<td>369 (234-502)</td>
<td>877 (498-1257)</td>
<td>861 (440-1281)</td>
</tr>
<tr>
<td>O₂ consumption</td>
<td>0.9% NaCl</td>
<td>90.6 (37.7-143.4)</td>
<td>213.3 (129.7-)</td>
<td>49.9 (35.5-64.3)</td>
<td>65.1 (39.6-90.6)</td>
</tr>
<tr>
<td>Parameter</td>
<td>0.9% NaCl</td>
<td>HES 130/0.4</td>
<td>0.9% NaCl</td>
<td>HES 130/0.4</td>
<td>0.9% NaCl</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>----------</td>
<td>------------</td>
<td>----------</td>
<td>------------</td>
<td>----------</td>
</tr>
<tr>
<td>(mL minute⁻¹ m²⁻¹)</td>
<td></td>
<td>71.8 (52.2-91.4)</td>
<td></td>
<td>245.9 (172.7-319.1)</td>
<td></td>
</tr>
<tr>
<td>O₂ extraction ratio (%)</td>
<td>9 (6-13)</td>
<td>51 (31-71)</td>
<td>9 (6-12)</td>
<td>10 (5-15)</td>
<td></td>
</tr>
<tr>
<td>Central venous O₂ saturation (mmHg)</td>
<td>96 (93-100)</td>
<td>52 (31-73)</td>
<td>100 (99-100)</td>
<td>98 (94-101)</td>
<td></td>
</tr>
<tr>
<td>Arteriovenous CO₂ difference (mmHg)</td>
<td>4.9 (2.9-6.9)</td>
<td>10.3 (4.2-16.4)</td>
<td>4.3 (0.0-8.5)</td>
<td>6.9 (5.3-8.5)</td>
<td></td>
</tr>
</tbody>
</table>

Comparisons were made for each parameter between groups at each time point. *Scheffe adjusted $p$ value < 0.05.
**Table 3** Mean and 95% confidence interval of acid-base variables in 12 anaesthetized greyhounds at four time points: T0, baseline; T1, during haemorrhagic shock, after removing 48 mL kg\(^{-1}\) of blood; T2, immediately after administration of 20 mL kg\(^{-1}\) of hydroxyethyl starch (HES) 130/0.4 or 80 mL kg\(^{-1}\) of 0.9% sodium chloride (NaCl) over 20 minutes; and T3, 40 minutes after completion of respective fluid administration.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pH</td>
<td>0.9% NaCl</td>
<td>7.39 (7.34-7.43)</td>
<td>7.36 (7.29-7.434)</td>
<td>7.24 (7.20-7.28)</td>
<td>7.33 (7.28-7.38)</td>
</tr>
<tr>
<td></td>
<td>HES 130/0.4</td>
<td>7.44 (7.42-7.46)</td>
<td>7.44 (7.40-7.48)</td>
<td>7.33 (7.25-7.41)</td>
<td>7.40 (7.37-7.43)</td>
</tr>
<tr>
<td>Hydrogen (nmol L(^{-1}))</td>
<td>0.9% NaCl</td>
<td>4.1 (3.7-4.5)</td>
<td>4.4 (3.7-5.1)</td>
<td>5.8 (5.2-6.3)</td>
<td>4.7 (4.1-5.3)</td>
</tr>
<tr>
<td></td>
<td>HES 130/0.4</td>
<td>3.6 (3.4-3.8)*</td>
<td>3.6 (3.3-3.9)</td>
<td>4.7 (3.8-5.6)*</td>
<td>4.0 (3.7-4.3)*</td>
</tr>
<tr>
<td>PaCO(_2) (mmHg)</td>
<td>0.9% NaCl</td>
<td>41 (39-44)</td>
<td>39 (35-44)</td>
<td>44 (42-45)</td>
<td>38 (35-42)</td>
</tr>
<tr>
<td></td>
<td>HES 130/0.4</td>
<td>39 (36-42)</td>
<td>34 (31-38)</td>
<td>44 (34-55)</td>
<td>43 (38-48)</td>
</tr>
<tr>
<td>------------------------</td>
<td>-------------</td>
<td>------------</td>
<td>------------</td>
<td>------------</td>
<td>------------</td>
</tr>
<tr>
<td>Bicarbonate (mmol L⁻¹)</td>
<td>0.9% NaCl</td>
<td>24 (21-28)</td>
<td>22 (19-24)</td>
<td>18 (16-20)</td>
<td>20 (18-22)</td>
</tr>
<tr>
<td></td>
<td>HES 130/0.4</td>
<td>26 (24-27)</td>
<td>23 (21-25)</td>
<td>22 (21-24)*</td>
<td>26 (24-28)*</td>
</tr>
<tr>
<td>Base excess (mEq L⁻¹)</td>
<td>0.9% NaCl</td>
<td>-0.1 (-3.4-3.3)</td>
<td>-2.9 (-6.2-0.4)</td>
<td>-8.2 (-10.6- -5.9)</td>
<td>-5.4 (-7.9- -2.8)</td>
</tr>
<tr>
<td></td>
<td>HES 130/0.4</td>
<td>2.6 (0.6-4.6)</td>
<td>0.0 (-1.8-1.8)</td>
<td>-3.1 (-4.9- -1.2)*</td>
<td>1.3 (-0.7-3.3)*</td>
</tr>
<tr>
<td>Chloride (mmol L⁻¹)</td>
<td>0.9% NaCl</td>
<td>116 (114-118)</td>
<td>118 (117-119)</td>
<td>128 (126-130)</td>
<td>125 (124-126)</td>
</tr>
<tr>
<td></td>
<td>HES 130/0.4</td>
<td>117 (115-119)</td>
<td>118 (117-120)</td>
<td>122 (120-125)*</td>
<td>120 (117-123)*</td>
</tr>
<tr>
<td>Lactate (mmol L⁻¹)</td>
<td>0.9% NaCl</td>
<td>1.0 (0.6-1.3)</td>
<td>1.5 (1.1-2.0)</td>
<td>0.8 (0.5-1.1)</td>
<td>0.8 (0.6-1.0)</td>
</tr>
</tbody>
</table>
Comparisons were made for each parameter between groups at each time point. *Scheffe adjusted $p$ value < 0.05. Statistical analysis was not performed on blood which included for the reader’s reference only.
Instrumentation

General anaesthesia (n = 12)

60 minutes

Haemorrhage

Shock (n = 12)

30 minutes

Fluid administration

20 mL kg⁻¹ HES 130/0.4 (n = 6)

20 minutes

End study

Fluid redistribution

80 mL kg⁻¹ 0.9% NaCl (n = 6)

40 minutes
Do you think the times written below is confusing? I put brackets in the 1st two to see if it helps the reader...? What do you think?

I feel "Fluid redistribution" may not be the right term.

And the distance between the vertical lines doesn't match the time frame. Do you think we should change the distance between the vertical lines to make it proportional to the time intervals?

Duana, 27-03-2015